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(54) Title: GELDANAMYCIN AND DERIVATIVES INHIBIT CANCER INVASION AND IDENTIFY NOVEL TARGETS

(57) Abstract: Geldanamycin derivatives that block the uPA-plasmin network and inhibit growth and invasion by glioblastoma cells and other tumors at femtomolar concentrations are potentially highly active anti-cancer drugs. GA and various 17-amino-17-demethoxygelddanamycin derivatives are disclosed that block HGF/SF-mediated Met tyrosine kinase receptor-dependent uPA activation at fM levels. Other ansamycins (macbecins I and II), GA derivatives, and radicicol required concentrations several logs higher (≥nM) to achieve such inhibition. The inhibitory activity of tested compounds was discordant with the known ability of drugs of this class to bind to hsp90, indicating the existence of a novel target(s) for HGF/SF -mediated events in tumor development. Methods of using such compounds to inhibit cancer cell activities and to treat tumors are disclosed. Such treatment with low doses of these highly active compounds provide an option for treating various Met-expressing tumors, in particular invasive brain cancers, either alone or in combination with conventional surgery, chemotherapy, or radiotherapy.